

## MEMORANDUM

## NOTE DE SERVICE

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TO  
A

Dr. J.E. Long,  
Chief,  
Toxicological Evaluation Division.

FROM  
DE

Dr. D.B. Davies,  
Section for Chemical Re-assessment,  
Toxicological Evaluation Division.

SECURITY - CLASSIFICATION - DE SÉCURITÉ

OUR FILE - N / RÉFÉRENCE

YOUR FILE - V / RÉFÉRENCE

DATE

September 14, 1982

SUBJECT  
OBJET

AUDIT AND VALIDATION OF THE STUDY: "THREE-GENERATION REPRODUCTION STUDY  
WITH DELNAV IN ALBINO RATS"\*

NAME OF LABORATORY:

Industrial Bio-Test Laboratories, Inc.,  
(Northbrook, IL)

LABORATORY REPORT NO.:

IBT No. 2476

REPORT DATE:

September 23, 1965\*

COMMON NAME OF COMPOUND:

Dioxathion

OTHER NAME(S):

Delnav, Deltic

FORM OF TEST MATERIAL:

Technical Grade (Form not specified)

PETITIONER:

BFC Chemicals, Inc. (Wilmington, Delaware -  
formerly Hercules Powder Co.)

TYPE OF STUDY:

3-Generation Reproduction

SPECIES, BREED AND STRAIN:

Rat

FILE UNDER:

Dioxathion

RECOMMENDATION PER AUDIT  
& VALIDATION:

Study invalid.

OVERALL COMMENTS:

The present study is adjudged invalid. Lack of adequate mating records precluded validation of the reported study findings. In this regard, the reproductive performance and progeny data provided resembled summary data in terms of presentation (tabular) and scope. These data were identified by cage number only, with lack of detail concerning mating date(s), sire number(s), dam number, confirmation of pregnancy and date of parturition. Further, for any given litter, details concerning selection of pups for future breeding were not given and individual pup numbers were not assigned. Thus, it was impossible to trace the linealogy of successive generations. Also, the possibility of biased selection of pups for breeding and occurrence of sibling matings could not be disclaimed. These deficiencies critically undermine the validity and usefulness of the study.

OVERALL COMMENTS - Continued

It should be noted that, owing to the lack of adequate mating records, the adequacy and accuracy of the raw data were not assessed in relation to the final report.

- \* This study was conducted simultaneously with 3-generation reproduction studies with norea (Herban) and toxaphene; the three studies shared two control groups. A series of reports pertaining to the study with Delnav were prepared by IBT, as follows:
  1. Three-Generation Reproduction Study in Albino Rats - Delnav - Results Through Weaning of F1b Litters, dated August 19, 1965.
  2. Progress Report - Three Generation Reproduction Study on Delnav - (Completion of F1 Generation), dated September 10, 1965.
  3. Final Report - Three Generation Reproduction Study on Delnav - (Termination - F2 Generation), dated September 23, 1965.
  4. Data Report - Three Generation Reproduction Study on Delnav - (Completion of F3a Litters), dated July 16, 1965.
  5. Progress Report - Three Generation Reproduction Study on Delnav - (Completion of F2 Generation), dated January 4, 1965.
  6. Data Report - Three Generation Reproduction Study on Delnav - (Completion of F1 Generation), dated July 16, 1965.

The sponsor offered no explanation to account for the apparent lack of sequence in the date order of the reports.

AUDIT

1. Report Title: "Three-Generation Reproduction Study with Delnav in Albino Rats" (see \* page 2).
2. Report Number and Date: IBT No. 2476  
Dated September 23, 1965  
(See \* page 2)
3. Dates of Study: Proposed starting date: Not specified - correspondence drafted by the sponsor (J.P. Frawley, Hercules to J.C. Calandra, IBT, October 17, 1963) authorized IBT to initiate the study "as soon as practical".  
Proposed termination date: Not specified.
4. Sponsor: Hercules Powder Company, Inc. (Wilmington, Delaware).
5. Protocol: A formal typewritten study protocol was not available. The sponsor simply advised IBT to conduct the study in accordance with the procedures outlined in the article entitled "Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics" (pp. 43-44), published by the Editorial Committee of the Association of Food and Drug Officials of the United States, 1959 (copy not provided - J.P. Frawley, Hercules to J.C. Calandra, IBT, Oct. 17, 1963). Specific details concerning treatment levels, mating schedules, pathological assessment and cholinesterase determinations were provided in the text of the above letter.  
  
Design modifications pertaining to clinical chemistry and cholinesterase determinations were authorized by the sponsor in letters dated Feb. 20, 1964 (J.P. Frawley to J.C. Calandra - frame 7), March 8, 1965 (J.P. Frawley to J. Kay - frame 11), and August 19, 1965 (J.P. Frawley to J.C. Calandra - frame 37).
6. Test Material: According to correspondence (J.P. Frawley to J.C. Calandra, Oct. 17, 1963), a 10 g sample of Delnav (purity not specified) was to be forwarded to IBT for test purposes. A shipping invoice was not available to confirm shipment and/or receipt of the test material at IBT.  
  
Additional correspondence (C.H. Wolf, IBT to J.P. Frawley, Nov. 10, 1964) shows a request for a further 10 g of test material to permit completion of the study. This correspondence references the initial sample as 'Delnav Technical Grade - Code X13622-78-3'.  
  
Diet preparation records show the use of Lot X13622-78-3 until January 13, 1965, followed by the use of Lot X14232-13. 3

7. Test Animals: Raw data show the use of male and female rats of unknown source or strain. Details concerning health status, selection criteria, housing conditions etc. were not available in the raw data.
8. Raw Data: Consist of correspondence, monthly cost sheets (January, 1964 to April-May, 1966), and original handwritten laboratory records. With regard to the latter, selected data were available for the following investigational parameters:

- (i) Mating Performance: These data were available as handwritten entries on laboratory notebook pages which were not dated or signed. The data resembled summary data in terms of presentation (tabular) and scope and included the following reproductive indices for each of the F<sub>0</sub>, F<sub>1</sub> and F<sub>2</sub> parental generations (2 litters/generation) for each treatment (i.e. Control I, Control II, Delnav-3 ppm or Delnav-10 ppm): mating index, fertility index, gestation time, incidence of pregnancy and incidence of parturition.

Individual data were identified by cage number only. Mating records for individual females (showing mating date(s), sire number(s), date of parturition etc.) were not available. Note that an additional set of data (designated "extra data") were presented for the F<sub>0</sub> generation.

- (ii) Progeny Data: These data were available as above and, again, resembled summary data in terms of presentation (tabular) and scope. Data were presented for the following indices for each of the F<sub>1</sub>, F<sub>2</sub> and F<sub>3</sub> litters for each treatment: number of pups delivered, number viable, number surviving to Day 1-5, -21, and pup body weights.

Note that duplicate records (compiled by different individuals) were provided for the F<sub>1a</sub> and F<sub>1b</sub> litters. Individual data were identified by cage number only. Individual pup numbers were not assigned, thereby precluding determination of lineal descent. Details concerning selection of pups for future breeding were not given.

- (iii) Diet Preparation: Records were available showing diet calculations, dates of preparation and quantities prepared. Data were initialled by appropriate technicians.
- (iv) Mortality: Summary data were presented in tabular form for each parental generation. Data were not signed or dated. Deaths were also recorded in the mating performance data. Pups deaths could be inferred from the progeny survival data.
- (v) Body Weights: Body weight and weight gain data (F<sub>1</sub> generation), weanling body weights (F<sub>2a</sub>, F<sub>2b</sub>, F<sub>3a</sub>, F<sub>3b</sub>), and sacrifice body weights (F<sub>2b</sub>) could be identified. Data were not signed or dated.

- (vi) Organ Weights: Selected data were presented in tabular form and were signed and dated.
- (vii) Pathology: Handwritten summary tables of histopathological findings (not signed or dated) were available. On occasion, data were not identified with respect to treatment and/or generation.
- (viii) Hematology: Raw data for the following hematological parameters were available for selected animals at termination: RBC count, WBC count, Hgb, Hct, differential leucocyte count, platelet count, reticulocyte count, prothrombin time, MCV, MCH and MCHC. Data were signed and dated.
- (ix) Clinical Chemistry: Raw data were provided for the following parameters for selected animals at termination: SGPT, OT, SAP, glucose, BUN and total and free cholesterol. Data were signed and dated.
- (x) Urinalysis: Raw data were available for the following parameters for selected animals: glucose, albumin, microscopic elements and pH.
- (xi) Cholinesterase Activity: Selected data were available which were signed and dated.

Despite the availability of the above records, the raw data are judged to be insufficient for validation owing principally to the absence of individual mating records. The mating performance and progeny data presented resemble summary data and do not permit 'tracking' of lineal descent due to lack of detail and improper animal identification.

It should be emphasized that, in view of the lack of adequate mating records, the adequacy and accuracy of the raw data provided were not assessed in relation to the final report.

#### OVERALL COMMENTS

The present study is adjudged invalid. Lack of adequate mating records precluded validation of the reported study findings. In this regard, the reproductive performance and progeny data provided resembled summary data in terms of presentation (tabular) and scope. These data were identified by cage number only, with lack of detail concerning mating date(s), sire number(s), dam number, confirmation of pregnancy and date of parturition. Further, for any given litter, details concerning selection of pups for future breeding were not given and individual pup numbers were not assigned. Thus, it was impossible

OVERALL COMMENTS - Continued

to trace the linealogy of successive generations. Also, the possibility of biased selection of pups for breeding and occurrence of sibling matings could not be disclaimed. These deficiencies critically undermine the validity and usefulness of the study.

It should be noted that, owing to the lack of adequate mating records, the adequacy and accuracy of the raw data were not assessed in relation to the final report.

OTHER AUDIT(S) AND VALIDATION(S):

An audit report for IBT No. 2476 (3-Generation Reproduction/Rat with Delnav) was prepared by John J. Domanski, Jr., Ph.D. (Toxicologist, Hercules Inc.) and dated 11/5/81. This report was supplemented with results of an additional audit performed by Pamela H. Errico (Deputy Director, Quality Assurance, Tracor Jitco) and Lorne A. Campbell, Ph.D. (President, Tracor Jitco). The company auditors concluded that the final report accurately reflected the raw data and adjudged the study valid. However, the lack of individual mating records noted herein was not alluded to in the company audit report.



D.B. Davies



J.E. Long